PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 943	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/IL2004/001095	International filing date *(day/month/year)* 30 November 2004 (30.11.2004)	Priority date *(day/month/year)* 30 November 2003 (30.11.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant YEDA RESEARCH AND DEVELOPMENT CO. LTD		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 07 June 2006 (07.06.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 740 14 35	Authorized officer Simin Baharlou Telephone No. +41 22 338 71 30

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL2004/001095	30.11.2004	30.11.2003

International Patent Classification (IPC) or both national classification and IPC
C07K16/40, A61P37/00, G01N33/50, A61K39/395, A61K31/7088

Applicant
YEDA RESEARCH AND DEVELOPMENT LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Ulbrecht, M Telephone No. +49 89 2399-7710

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IL2004/001095

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-5,11-15,21-33,59 (all partially);21-38 (with resepect to IA)

because:

☒ the said international application, or the said claims Nos. 21-38 (with resepect to IA) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-5,11-15,21-33,59 (all partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-43,45-58
	No:	Claims	44,59
Inventive step (IS)	Yes:	Claims	1-10,21-28,45-58
	No:	Claims	11-20,29-44
Industrial applicability (IA)	Yes:	Claims	1-25,39-59
	No:	Claims	

2. Citations and explanations

see separate sheet

Re item III:

1.1 Claims 1-5, 11-15 and 21-33 refer to compounds which are only functionally defined, namely by their ability to increase or increase NIK-SIVA complex formation, to increase or decrease NIK-dependent CD27 regulation, and to decrease or increase the activity of NIK. These compounds are not structurally defined and only few instances of such compounds are disclosed by the present application. Moreover, it is not determinable which compounds are covered by the said functional definitions, thereby rendering the scope of said claims unclear to such an extent as to render a meaningful search thereof impossible (Art. 6 PCT). Consequently, inasmuch as these compounds are concerned said claims were only searched with respect to the specific compounds falling under said functional definitions, namely those referred to in claims 6-10, 39-41 and 44-46.

1.2 Claims 2, 11-15, 22 and 29-33 refer to diseases that are defined functionally by reference to the expression or function of BlyS/BAFF, CD27, SIVA and NIK (claims 2 and 22); or to abnormal NF-κB activation via the canonical pathway (claims 11-15 and 29-33), in particular related to CD70 (claims 13 and 32), CD40L (claims 14 and 31), BlyS (claims 15 and 33) and the respective receptors. As it is unclear which diseases fall under these definitions a meaningful search over the whole scope of said claims is not impossible (Art. 6 PCT). The search was therefore limited to the diseases according to claims 3 and 23.

1.3 Claim 59 refers to compounds that are identified by a method of screening. These compounds are not limit by any structural features. No defined compounds are disclosed which were identified by the said screening method. A meaningful search of the said claim is therefore not possible (Art. 6 PCT). The only instances of such compounds which might fall under the scope of claim 59 disclosed by the present application are those of claims 39-41 and 44-46. The search was thus limited to these compounds.

2. The substantive examination referred to under item V. herein below is restricted to searched subject-matter (R. 66.1(e) PCT).

3. Claims 26-38 relate to subject-matter considered by this Authority to be covered by the provisions of R. 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT).

Re item V:

1. Reference is made to the following documents:

D1: WO 03/087380 A (YEDA RESEARCH AND DEVELOPMENT CO.LTD; WALLACH, DAVID; RAMAKRISHNAN, PA) 23 October 2003 (2003-10-23)

D2: CHRISTMAN J W ET AL: "Nuclear factor kappa B: a pivotal role in the systemic inflammatory response syndrome and new target for therapy." INTENSIVE CARE MEDICINE. NOV 1998, vol. 24, no. 11, November 1998 (1998-11), pages 1131-1138

D3: LIN X ET AL: "MOLECULAR DETERMINANTS OF NF-KAPPAB-INDUCING KINASE ACTION" MOLECULAR AND CELLULAR BIOLOGY, AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON, US, vol. 18, no. 10, October 1998 (1998-10), pages 5899-5907

D4: WO 98/54323 A (DANA-FARBER CANCER INSTITUTE) 3 December 1998 (1998-12-03)

D5: WO 97/37016 A (YEDA RESEARCH AND DEVELOPMENT CO. LTD; WALLACH, DAVID; MALININ, NIKOLA) 9 October 1997 (1997-10-09)

D6: US-A-5 843 721 (ROTHE ET AL) 1 December 1998 (1998-12-01)

2. *Novelty (Art. 33(2) PCT):*

2.1 D1 discloses antibodies directed at fragments of NIK comprising amino acid residues 624-947 and 640-720 (claims 43-49). Hence, claims 44 and 59 lack novelty over D1.

2.2 The subject-matter of claims 1-43 and 45-58 is novel as the combination of features suggested by each of said claims is not disclosed in the prior art.

3. *Inventive step (Art. 33(3) PCT):*

3.1 D2 suggests the use of compounds that antagonise or block NIK in the treatment of ia. SIRS, MODS and ARDS (p. 1134, c. 2, last para.). As the NIK protein and gene are already known in the art (cf. D6), the skilled person in applying his routine knowledge would use the compounds suggested by claims 16, 18 and 20 in order to set the teaching of D2 into practice. Hence, the subject-matter of claims 11 and 29 lacks an inventive step in view of D2.

3.2 For the same considerations also the subject-matter of claims 12-16, 18, 19, 30-34, 36 and 38-40 appears to lack an inventive step over D2.

3.3 Claims 19, 37 and 41 suggest an apparently arbitrarily selected siRNA molecule targeting NIK which does not bring about any unforeseeable technical effect beyond the foregoing considerations and which therefore also apply to the said claims.

3.4 D3 taches the importance of the phosphorylated NIK activation loop for the function of NIK (abstract). The skilled person would therefore be prompted by D3 to specifically select an antibody directed at said loop when setting the teaching of D2 into practice. Hence, the subject-matter of claims 17 and 35 is considered not inventive.

3.5 Since the nucleic acid according to claim 39 is not considered inventive (cf. V 3.1 and 3.2) and the further technical features according to claims 42 and 43 are based on routine experimentation without resulting in any unforeseeable technical effect, the latter claims are also not considered inventive.

3.6 The subject-matter of claims 1 and 4 is distinguished from D2 representing the closest prior art in that the pathways on which the therapeutic effect is based, being either a modulation of NIK-SIVA complex formation or of NIK-dependent CD27 regulation, are defined. The technical problem thus resides in providing a treatment for immune disorders by defined cellular pathways. No prior art document teaches an association of NIK with SIVA or of NIK being involved in CD27-mediated signalling and in particular not in the context of immune disorders. Hence, the solutions provided by claims 1 and 4 are considered to involve an inventive step.

3.7 These considerations also apply to claims 21 and 26 as well as to dependent claims 2-3, 5-10, 22-25 and 27-28.

3.8 Claims 45 and 46 suggest antibodies which specifically inhibit the formation of NIK-SIVA complexes. D4 teaches SIVA1 and SIVA2 specific antibodies, no preference with respect to the targeted region within said proteins is disclosed. The technical problem thus resides in providing SIVA specific antibodies which interfere with NIK-SIVA complex formation. As the association of NIK and SIVA is not known from the prior art, the skilled person would not have an incentive to target any specific region of SIVA1 or SIVA2 and the subject-matter of claims 45 and 46 thus involves an inventive step.

3.9 Claims 47-49 and 54 provide methods which aim at identifying compounds which modulate different targets of the NIK-mediated signalling pathway. Although D5 teaches a method of identifying compounds modulating the cellular activity modulated/mediated by NIK, contrary to the foregoing claims, it does not suggested any specific targets used in the analyses. The prior art is also silent in general with respect to the targets suggested by said claims as being involved in NIK-dependent signalling. The application discloses the different NIK-mediated signalling events addressed in said claims. Hence, these claims are considered inventive.

3.10 The same considerations also apply to dependent claims 50-53 and 55-58.

4. *Industrial applicability (Art. 33(4) PCT):*

4.1 For the assessment of the present claims 26-38 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4.2 The subject-matter of claims 1-25 and 39-59 appears to be industrial applicable.